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09/761,893	01/17/2001	Shih-Chieh Hung	11709-003001	6011

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Shih-Chieh Hung
Dept. of Orthop. and Traumatology, Vet. General
201, Sec. 2, Shih-pai Road
Hospital-Taipei
Taipei, 11217
TAIWAN

EXAMINER

DUNSTON, JENNIFER ANN

ART UNIT	PAPER NUMBER
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1636

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/761,893	Applicant(s) HUNG ET AL.	
	Examiner Jennifer Dunston	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 October 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4,6,9-20 and 33-38 is/are pending in the application.
- 4a) Of the above claim(s) 12-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4,6,9-11 and 33-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 January 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/5/2009 has been entered.

Receipt is acknowledged of an amendment, filed 10/5/2009, in which claim 32 was canceled, and claims 1 and 34-38 were amended. Claims 1, 4, 6, 9-20 and 33-38 are pending.

It is noted that claims 39 and 40 are listed as canceled, as required by the Office letter mailed by Cordelia Betancourt on 9/24/2009. It is noted that claims 39 and 40 were never entered. In order to maintain the integrity of the electronic file, these claims will be considered as canceled claims. It is not necessary for Applicant to provide the text of the canceled claims. For example, listing the following is sufficient: claims 39-40 (Canceled).

Election/Restrictions

Applicant elected Group I without traverse in the reply filed on 9/4/2001.

Claims 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 9/4/2001.

Currently, claims 1, 4, 6, 9-11 and 33-38 are under consideration.

Claim Objections

Claim 38 is objected to because of the following informalities: the phrase "4.time.10.sup.3-10.sup.4/cm.sup.2" should be changed to $4 \times 10^3\text{-}10^4/\text{cm}^2$ to use terminology consistent with that disclosed in the as-filed specification. Appropriate correction is required.

Response to Arguments - Claim Objections

The previous objections of claims 1, 4, 6, 9-11 and 32-38 have been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6, 9-11 and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection, necessitated by the amendment of claim 1 in the reply filed 10/5/2009.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

Art Unit: 1636

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method for isolating mesenchymal stem cells (MSCs) from bone marrow aspirate, and the claims explicitly require the separation of MSCs from hematopoietic stem cells (HSCs).

Independent claim 1 comprises the following method steps: (a) providing a cell mixture comprising MSCs and other cells; (b) seeding and culturing the cell mixture in a culture device comprising an upper plate with pores and a lower plate base, said upper plate made of MSC adhering material, where MSCs adhere and are cultured, and the lower plate base, where the other small-sized HSCs adhere following passing through the pores in the upper plate, said culturing with medium containing factors that stimulate MSC growth without differentiation and allows for the selective adherence of only MSCs to the upper plate surface; and (c) removing non-adherent cells on the upper plate by changing medium. Dependent claims 4, 6 and 9 further limit the characteristics of the MSC. Claims 11 and 35-38 further limit the culturing conditions. Claim 11 is drawn to the use of culture medium comprising 10% fetal bovine serum-supplemented Dulbecco's modified Eagle's medium containing 1g/L of glucose. Dependent claim 33 limits the pore size to about 0.4 to 40 microns in diameter. Dependent claim 34 limits the mesenchymal stem cell adhering material to plastic.

The claimed invention seeks to exploit the biological and physical characteristics of MSCs to provide an isolated population of MSCs. With regard to the biological properties, the claim requires the selective adherence of MSCs to the top plate. With regard to physical properties, the claim requires size selection of MSCs. Specifically, the upper plate with pores

Art Unit: 1636

must separate MSCs from HSCs. The upper plate must retain the MSCs while allowing HSCs to pass through the pores.

Breadth of the claims: The claims broadly encompass the use of a culture device comprising an upper plate that contains pores of any size. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions using the physical and biological characteristics of MSCs to isolate MSCs from a cell mixture. Specifically, the specification envisions using a difference in cell size and a difference in adherence to isolate MSCs (e.g., page 7, lines 10-17). The specification envisions using a plate with pores, where the pore size is defined functionally as being "sufficient for separating mesenchymal stem cells from other cells (e.g. haematopoietic stem cells)" (page 7, lines 24-27). The specification asserts that a preferable pore size is from about 0.4 to 40 microns in diameter (e.g., page 7, lines 27-29; page 8, lines 29-30).

A working example of the claimed method is presented on page 11-12 of the specification; however, the working example **does not disclose the pore size** of the upper plate. Percoll fractionated or un-fractionated bone marrow cells in DMEM-LG with 10% FBS and antibiotics were seeded into a culture device at a density of $10^6/\text{cm}^2$ (page 11, lines 20-25). The design specifics of the culture device used in the working example are not disclosed. The specification notes that HSCs and non-adherent cells were removed with changes in medium (page 12, lines 4-6; page 14, lines 18-20). The cells retained by the upper plate were analyzed and found to have characteristics consistent with a MSC phenotype (e.g., page 12, line 16 to page 15, line 28). At page 14, the specification discusses the characteristics of the cells that are

Art Unit: 1636

collected on the bottom plate (i.e., the cells that pass through the undefined pores). The cells were described as having a small size, polygonal shape, and little renewal capacity (page 14, lines 7-9). The specification states that the cells "were believed to be haematopoietic cells" (page 14, line 10).

The specification does not provide any characterization of the cells that are collected on the lower plate and are "believed to be haematopoietic cells." The cell surface markers of the cells were not analyzed (e.g., CD34). The ability of the cells to differentiate along the hematopoietic lineage or perform hematopoietic reconstitution is not disclosed.

Predictability and state of the art: The state of the art with regard to the separation of MSCs and HSCs based upon size selection through pores was underdeveloped at the time the invention was made. Prockop et al (US Patent No. 7,374,937 B1, effective date March 14, 2000, cited in a prior action) teaches the isolation of MSCs from bone marrow aspirates obtained from the iliac crest of normal human donors (e.g., column 24, line 24 to column 35, line 5). The non-adherent cells were removed, and the adherent cells were harvested (e.g., paragraph bridging columns 34-35). Prockop et al assayed the MSCs for size and granularity by forward light and side light scattering by FACS (e.g., column 36, lines 9-41). When the MSCs were plated at a low density, a population of large cells with a medium content of granules was observed (mature MSCs or mMSCs) along with two populations of small cells: (1) small and agranular cells referred to as recycling stem cells-1 (RS-1); and (2) small and granular cells referred to as recycling stem cells-2 (RS-2) (e.g., column 36, lines 31-34). Prockop et al teach that a polycarbonate membrane with a pore size of 10 micrometers separates the mMSCs from the RS cells (e.g., column 39, line 60 to column 40, line 42). Prockop et al teach that the small cells that

Art Unit: 1636

pass through the pores are CD34-negative (e.g., Figure 26). The present specification teaches that HSCs obtained from bone marrow are CD34-positive (e.g., page 14, lines 26-27). Thus, the small cells separated from the MSC of bone marrow aspirate using a 10 micron filter do not appear to be HSCs. Further evidence that the small cells are not HSCs is provided by the post filing art. Colter et al teach that the RS cells are capable of adopting the same cell fates as MSCs in that they are capable of differentiating into osteoblasts, adipocytes and cartilage (Colter et al. Proceedings of the National Academy of Sciences, USA, Vol. 98, No. 14, pages 7841-7845, July 2001; e.g., paragraph bridging pages 7843-7844). Accordingly, it would be unpredictable to use a filter containing pores of 10 micrometers to separate MSCs from HSCs of bone marrow aspirate.

Applicant's own post-filing art teaches that MSCs were isolated from human bone marrow aspirates by the use of a "unique method that included a specially designed culture device, which was a plastic culture dish comprising a plate with 3- μ m pores to sieve out MSCs from bone marrow aspirates" (Hung et al. Stem Cells, Vol. 20, pages 249-258, 2002; e.g., page 250, right column). The specific culture device used was a 10-cm plastic culture dish comprising a plate with 3- μ m pores sold as a Transwell® device by Corning Inc. (e.g., page 251, paragraph bridging columns). The features of this device, such as the 3- μ m pore size, are not taught by the present specification.

The post filing art teaches that the cells collected on the lower plate base have never been characterized (Zuba-Surma et al. Cytometry Part A, Vol. 75A, pages 4-13, 2009; e.g., page 11, right column, last full paragraph). Given the lack of characterization of the small cells, and the evidence provided by Prockop et al and Colter et al that other small cells present in bone marrow

Art Unit: 1636

are not HSCs, it would be unpredictable to separate MSCs from HSCs using a device with any size pores, or pores ranging from 0.4-40 microns.

Amount of experimentation necessary: The quantity of experimentation needed to carry out the claimed invention is large. One would be required to determine the pore sizes that provide separation of MSCs from HSCs obtained from bone marrow aspirate. The prior art teaches that pores of 10 μm do not separate MSCs from HSCs; rather, pores of 10 μm separate large MSCs from small MSCs (RS cells). Furthermore, the specification does not teach the pore sized used in the working example. Without the guidance of the post filing art, it would require a large amount of experimentation to determine the pore size that provides the result obtained in the specification. The post-filing art teaches a pore size of 3 μm was used, and the specification discloses any pore size, or preferably about 0.4 to 40 μm . Even if one were to use a pore size of 3 μm , there is no evidence on the record that the small cells obtained on the lower plate are HSCs. To determine if the cells are HSCs, one would be required to determine the cell surface markers and test the ability of the cells to differentiate along the hematopoietic lineage or perform hematopoietic reconstitution. The outcome of any experiment relying upon the guidance of the specification and prior art is unpredictable, and the type of experimentation required is not routine in the art.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 4, 6, 9-11 and 33-38 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

The rejection of claims 36-38 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

Response to Arguments - 35 USC § 103

The rejection of claims 1, 4, 6, 9, 11, 32, 33 and 35-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Rieser et al and Burkitt et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Rieser et al and Burkitt et al, and further in view of Pittenger et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claims 1, 4, 6, 9, 11, 32 and 35-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Butz et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Butz et al, and further in view of Pittenger et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claim 33 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Butz et al, and further in view of Pall has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claims 1, 4, 6, 9, 11 and 32-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Prockop et al and Matsui et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claims 1, 4, 6, 9, 11 and 32-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Burkitt et al and Mussi et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

The rejection of claims 1, 4, 6, 9, 11, 32 and 34-38 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Guirguis and Matsui et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/5/2009.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

Art Unit: 1636

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/Jennifer Dunston/
Examiner
Art Unit 1636